REMARKS

Claims 5-10, 37-40, and 42-54 were pending in the instant application. In the Office Action mailed November 28, 2007 (hereinafter "Office Action"), claims 5-10, 37-40, and 42-54 are rejected. Claims 5, 7, 38, 39, 44, 45, 50, and 51 are canceled without prejudice. Claims 6, 8, 10, 40, 42, 43, 46, 47, 49, 53, and 54 are amended. New claims 55-57 are added. Upon entry of this amendment, claims 6, 8-10, 37, 40, 42, 43, 46-50, and 53-57 will be pending.

Claim 6 has been amended to replace "sequential cycles of synthesis" with "different cycles of synthesis." Support for the amendment is found, for example, at page 18, line 13 of the specification. Claim 6 has been amended to recite "wherein each of said quality control probes optionally further comprises a first sequence contiguous with said predetermined binding sequence." Support for the amendment is found, for example, at Figures 2A and 2B and page 43, lines 20-23 of the specification. Step (b) of claim 6 has also been amended to replace (i) with (1) and to replace (ii) with (2) for purposes of clarity and to avoid confusion. Claim 6 has also been amended for consistency of language and to correct a grammatical error.

Claim 8 has been amended for clarity and to be consistent with the language of claim 6.

Claims 10, 43 and 49 have been amended to replace (i) with (A) and to replace (ii) with (B) for purposes of clarity and to avoid confusion.

Claims 40 and 54 have been amended to recite "wherein said periodicity of P is equal to the number of nozzles in an inkjet printhead." Support for the amendment is found, for example, at page 20, lines 19-25 of the specification.

Claim 40 has been amended to replace "sequential cycles of synthesis" with "different cycles of synthesis." Support for the amendment is found, for example, at page 18, line 13 of the specification. Claim 40 has been amended to recite "two or more quality control probes of said plurality of quality control probes that are arranged in said periodicity of P." Support for the amendment is found, for example, at page 6, lines 25-26 of the specification. Claim 40 has also been amended for consistency of language and to correct a grammatical error.

Claims 42, 43, and 46 have been amended such that they depend upon claim 40 instead of the canceled claim 5. Support for the amendment is found, for example, at page 7, lines 7-11 and page 4, lines 13 of the specification. Claim 47 has been amended to replace "sequential cycles of synthesis" with "different cycles of synthesis." Support for the amendment is found, for example, at page 18, line 13 of the specification. Claim 47 has been

amended to recite: "wherein the sequence of each quality control probe in said plurality of quality control probes consists of (i) the same predetermined binding sequence or (ii) a different predetermined binding sequence with the same binding specificity, the synthesis of said predetermined binding sequence in each said quality control probe having been initiated during said step-by-step synthesis at different cycles of synthesis of staggered start, wherein said respective different cycles of synthesis of staggered start are initiated at every progressive synthesis cycle during synthesis of the array." Support for the amendment can be found, for example, at page 4, line 31; page 18, line 13; page 19, lines 13-15; Figures 3A and 3B; and page 46, lines 26-27 of the specification. Claim 47 has also been amended for clarity and consistency of language and to correct a grammatical error.

Claim 49 has been amended to replace (i) with (A) and to replace (ii) with (B) for purposes of clarity and to avoid confusion.

Claims 51 and 53 have been amended for clarity and for consistency of language.

Claim 54 has been amended to replace "sequential cycles of synthesis" with "different cycles of synthesis." Support for the amendment is found, for example, at page 18, line 13 of the specification. Claim 54 has been amended to recite: "wherein the sequence of each quality control probe in said plurality of quality control probes consists of (i) the same predetermined binding sequence or (ii) a different predetermined binding sequence with the same binding specificity, the synthesis of said predetermined binding sequence in each said quality control probe having been initiated during said step-by-step synthesis at different cycles of synthesis of staggered start, wherein said respective different cycles of synthesis of staggered start are initiated at every progressive synthesis cycle during synthesis of the array." Support for the amendment can be found, for example, at page 4, line 31; page 18, line 13; page 19, lines 13-15; Figures 3A and 3B; and page 46, lines 26-27 of the specification. Claim 54 has been amended to recite "are arranged in said periodicity of P." Support for the amendment is found, for example, at page 6, lines 25-26 of the specification. Claim 54 also has been amended for clarity and consistency of language and to correct a grammatical error.

New claim 55 is added. Support for claim 55 is found, for example, page 20, lines 19-25 of the specification.

New claim 56 is added. Support for claim 56 is found, for example, at page 4, lines 30-31; page 6, lines 1-33; page 20, lines 19-25; and Figures 3A-3B of the specification.

New claim 57 is added. Support for claim 57 is found, for example, at page 20, lines 19-25 of the specification.

No new matter has been added by these amendments. Entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

THE OBJECTIONS TO THE CLAIMS SHOULD BE WITHDRAWN

In the Office Action, the Examiner advised Applicants "that should claims 47-53 be found allowable, claims 5, 7, and 42-46 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof" (Office Action, page 2, fifth paragraph). Specifically, the Examiner contends that:

> [c]laims 5 and 47 appear to cover the same breadth. Claims 42 and 48 are verbatim. Claims 43-46 and claims 48-52 are verbatim. Claim 7 and claim 53 are verbatim.

(Office Action, page 2, sixth paragraph). Applicants respectfully disagree.

While believing that the Examiner's contention is incorrect, Applicants have nevertheless canceled claims 5, 7, and 45 and have amended claims 42, 43, and 46 to depend on claim 40, in order to expedite prosecution. As such, the Examiner's objection to claims 5, 7, and 42-46 has been rendered moot.

Accordingly, Applicants respectfully request that the Examiner's objection to claims 5, 7, and 42-46 be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 112 of CLAIMS 6, 8-10, 37-40, AND 45-54 SHOULD BE WITHDRAWN

In the Office Action, claims 6, 8-10, 37-40, and 45-54 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention (Office Action, page 3, third paragraph). Applicants respectfully disagree.

The Examiner contends that claim 6 is indefinite because:

> [c]laim 6 recites that at least some of quality control probes differ from other of said quality control probes in the length of said first sequence, but recites that these first sequences can be a number ranging from ***0***. Since the claim predefines (based on Applicants' election) that all of the quality control probes have the ***same*** predetermined binding sequences [*sic*], it is unclear how the length of some of these quality control probes can be different if there are ***no*** first sequence [*sic*] appended thereto. For the purpose of prosecution, the first sequence can be a number ranging from 1 to N monomers, wherein N is greater or equal to 2.

(Office Action, page 3, fifth paragraph). The Examiner further contends that "[c]laims 8-10 and 37-39 are indefinite by way of their dependency on claim 6" (Office Action, page 3, sixth paragraph).

Firstly, Applicants respectfully point out that the instant claim 6 does not specify that "all of the quality control probes have the same predetermined binding sequence;" instead, claim 6 recites "each quality control probe in said plurality of quality control probes comprising (i) the same predetermined binding sequence ***or*** (ii) a different predetermined binding sequence with the same binding specificity" (emphasis added). In fact, Applicants had elected, in response to the restriction requirement issued on July 11, 2007, species (ii) a different predetermined binding sequence with the same binding specificity.

Secondly, Applicants respectfully point out that step (b) of instant claim 6 recites "detecting or measuring binding between (1) two or more quality control probes of said quality control probes that ***differ*** in the number of said monomers; and (2) said binding partner in the sample" (emphasis added). Thus, pursuant to the claim language, when a quality control probe that has no first sequence (there is no sequence of monomers contiguous to its predetermined binding sequence; i.e., the number of monomers is zero) is detected and measured in step (b), it will be compared in step (c) with another quality control probe which ***has*** a first sequence, because the language of claim 6 requires that the binding of quality control probes that ***differ*** in the number of the monomers be compared. Thus, one quality control probe used in step (b) can have $N = 0$, but then others of said two or more quality control probes referenced in step (b) must have $N \neq 0$ and thus N being a whole number greater than or equal to 1. As such, the Examiner's contention that claim 6 is indefinite is without merit. Accordingly, the Examiner's contention regarding the indefiniteness of claims 8-10 and 37-39 due to their dependency on claim 6 also is without merit.

Claim 8, as previously presented, recited the phrase "two of said two or more quality control probes." The Examiner contends that:

> [t]he parent claim 6 clearly recites that there are two types of quality control probes – the ones with first sequences in addition to the predetermined binding sequences and [the] ones without.
>
> Therefore, it becomes confusing which of the quality control probes the limitation is referring to.

(Office Action, page 3, paragraphs 7 and 8). Applicants respectfully disagree.

Claim 8 clearly recites "two [quality control probes] of said two or more quality control probes." Antecedent basis for "said two or more quality control probes" is provided in claim 6, step (b), which states that the "two or more" "differ in the number of said

monomers" [N]. Thus, clearly, the two quality control probes in claim 8 are from the subset of quality control probes that differ in the number of the monomers (N) in their first sequences. Accordingly, since for the two quality control probes N must differ, one of the two must have N greater than zero, while the other can have N = 0, or N being greater than zero as long as it is not the same as the N of the first probe. As such, the phrase "two or more quality control probes of said two or more quality control probes" is clear. In addition, Applicants have amended claim 8 for purposes of clarity such that the phrase "two of said two or more quality control probes" now reads "two quality control probes of said two or more quality control probes." As discussed above, the meaning of the phrase "two quality control probes of said two or more quality control probes" is clear in light of the antecedent basis provided in step (b) of claim 6. Thus, the Examiner's contention that claim 8 is indefinite is without merit.

The Examiner states that claims 38, 40, 45, 51, and 54 define that the quality control probes are arranged in a periodicity having the variable of "P," and also assign the number of nozzles the same variable, "P." The Examiner contends that "the phrase which recites, 'where P is a whole number equal to or greater than 1,' becomes confusing as to which of the two (periodicity or number of nozzles) it is referencing to" (Office Action, page 4, first paragraph). The Examiner further contends that "[c]laims 39, 46, and 52 are indefinite for analogous reasons" (Office Action, page 4, second paragraph). Applicants respectfully disagree.

Applicants have amended claims 40 and 54 to recite "wherein said periodicity of P is equal to the number of nozzles in an inkjet printhead." The periodicity of P is defined by the number of nozzles in an inkjet printhead; therefore, it is clear that the same variable P is both the periodicity of P and the number of nozzles in the inkjet printhead. As such, claims 40 and 54 are clear. Claim 46 has been amended to depend from claim 40. Claims 38, 39, 45, 51, and 52 have been canceled. Thus the Examiner's rejection is obviated.

The Examiner further contends that:

> [c]laim 47 is indefinite because the claims at one point recites the phrase, "said plurality of control probes comprising (i) the same predetermined binding sequence..." then later recites that the same "said [quality] control probes consists [*sic*] of said predetermined binding sequence."

(Office Action, page 4, third paragraph). Thus, the Examiner contends that "[i]t is confusing whether the control probes 'comprises' or 'consists' of a predetermined binding sequence" (Office Action, page 4, fourth paragraph). The Examiner

further contends that "[c]laims 48-53 are indefinite by way of their dependency on claim 47" (Office Action, page 5, fifth paragraph).

Applicants respectfully point out that the amended claim 47 recites "wherein the sequence of each quality control probe in said plurality of quality control probes ***consists of*** (i) the same predetermined binding sequence or (ii) a different predetermined binding sequence with the same binding specificity" (emphasis added). In addition, the limitation of "wherein the sequence of each quality control probe in said plurality of quality control probes consists of said predetermined binding sequence" has been deleted from claim 47 as redundant in view of the amended claim recitation. As such, the Examiner's contention that the usage of the phrases "comprising" and "consists of" in claim 47 is confusing has been rendered moot in light of the amendments.

Accordingly, Applicants respectfully request that the rejection of claims 6, 8-10, 37-40, and 45-54 under 35 U.S.C. § 112, second paragraph, be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 102 of CLAIMS 5, 6, 9, 42, 47, 48, AND 54 SHOULD BE WITHDRAWN

Claims 5, 6, 9, 42, 47, 48, and 54 are rejected under 35 U.S.C. § 102 as being anticipated by United States Patent No. 6,130,046, issued to Hubbell et al. on October 10, 2000 (hereinafter "Hubbell") (Office Action, page 4, eighth paragraph). Applicants respectfully disagree.

The Examiner contends that Hubbell generally discloses a method of determining the quality of the synthesis of an array that comprises each of the three steps recited in claims 5, 9, 42, 47, and 48 (Office Action, page 5, paragraphs 1-3). With regard to claim 6, the Examiner further contends that Hubbell anticipates "the invention as claimed when the first sequence is interpreted with zero being the integer" (Office Action, page 5, fourth paragraph).

Firstly, Applicants respectfully point out that claim 5 has been canceled without prejudice. Thus, the rejection of claim 5 has been rendered moot.

Secondly, as discussed hereinabove, amended claim 6 teaches "detecting or measuring binding between (1) two or more quality control probes of said plurality of quality control probes that ***differ*** in the number of said monomers; and (2) said binding partner in the sample" (emphasis added). According to this limitation of claim 6, ***at least*** one of the two or more quality control probes has a number of monomers that is ***not*** equal to zero and thus a contiguous first sequence (e.g., a spacer sequence as depicted in Figures 2A and 2B) is present. Thus, a spacer sequence is present in one or more of the quality control probes

whose binding is compared in step (c) of claim 6. Thus, steps (b) and (c) of claim 6 are always carried out by using at least one quality control probe that has a spacer sequence. For example, the comparison of step (c) is always carried out between a quality control probe with a spacer sequence (i.e., having 1 to N monomers) and a quality control probe with no spacer (i.e., having zero monomers) **or** between two quality control probes both containing spacer sequences that are of different monomer numbers greater than zero.

As such, claim 6 is distinguished over Hubbell in that Hubbell does not disclose the use of arrays containing quality control probes with spacers. Hubbell also does not disclose detecting or measuring binding between two or more quality control probes and its binding partners in a sample where at least one of the two or more quality control probes has a spacer sequence contiguous to its predetermined binding sequence. Hubbell further does not disclose comparing binding of the two or more quality control probes where at least one of the two or more quality control probes has a spacer sequence contiguous to its predetermined binding sequence. Therefore, claim 6 is not anticipated by Hubbell.

Claim 42 has been amended to depend from non-rejected claim 40, thus obviating the rejection of claim 42.

The amended claim 47 recites:

> wherein the sequence of each quality control probe in said plurality of quality control probes consists of (i) the same predetermined binding sequence or (ii) a different predetermined binding sequence with the same binding specificity, the synthesis of said predetermined binding sequence in each said quality control probe having been initiated during said step-by-step synthesis at different cycles of synthesis ***of staggered start, wherein said respective different cycles of synthesis of staggered start are initiated at every progressive synthesis cycle during synthesis of the array***, and wherein said sample comprises a binding partner that binds said predetermined binding sequence

(emphasis added). Claim 47 thus specifies that quality control probes are synthesized with staggered start in the different cycles of synthesis, initiated at every progressive synthesis cycle during synthesis of the array.[1] Figure 3A of the application provides an illustration of an exemplary embodiment of the array of claim 47. Such quality control probes synthesized with staggered start in their respective different cycles of synthesis, initiated at every progressive cycle, is not taught or suggested by Hubbell. The synthesis of polymer probes as disclosed in Hubbell ***fundamentally*** differs from that disclosed in the instant claims. The

[1] Applicants point out that "during synthesis of the array" is clearly understood as during synthesis of the non-quality control probes of the array (see specification at page 46, lines 25-29), since to construe the term otherwise would mean synthesis is never ending, since endless cycles would occur.

teaching of Hubbell relies upon synthesizing a microarray by a photolithographic patterning method. In this method, probes on the microarray are synthesized by monomer addition cycles that are arranged in a predetermined order (*e.g.*, see cycles in Figures 6-7 and the "control sequence of monomers" in box 301 in Figure 9 of Hubbell). If a particular monomer addition cycle is utilized in synthesizing multiple probes, the same type of monomer will added to ***each*** of the multiple probes; *i.e.*, the common synthesis cycle. Whether a monomer will be added to a probe in a particular monomer addition cycle will be determined by a pre-designed mask. Only the locations on the microarray that are photolithographically de-protected will receive the common monomer. For more details on the photolithographic patterning method for microarray, see, for example, in United States Patent Number 5,143,854 issued on September 1, 1992 to Pirrung et al., which is cited in Hubbell and concurrently submitted herewith in the Supplemental Information Disclosure Statement as reference No. A12. See also, for example, Hubbell, at column 4, line 37 through column 4, line 55; column 6, lines 6-39; and Figures 3 and 5-9. Figure 9 of Hubbell provides a general outline of how control probes may be designed based on a control sequence of monomers consisting of predetermined nucleotide addition cycles (e.g., a repeating nucleotide addition cycle such as ACGT). The concepts of control probe design and their application in evaluating the integrity of the synthesis process are further illustrated in Figures 6-8.

In a specific example as described in Hubbell, a probe of 3'-ACGT may be synthesized by a synthesis cycle ACGTACGT in a number of different ways as follows:

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ACGTACGT          (cycles)
ACGT              (probe 1)
AC    GT          (probe 2)
    ACGT          (probe 3)
ACG    T          (probe 4)
A    CGT          (probe 5)
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See Hubbell, column 6, line 40 through column 7, line 30. Here, ACGTACGT is the predetermined order of the monomer addition cycles or the control sequence of monomer; *i.e.*, nucleotides will be added in this particular order throughout the synthesis cycle of the probes. The predetermined order of the monomer addition cycles consists of repeating cycles of ACGT. Thus, as shown above, Hubbell does disclose quality control probes of staggered start (e.g., probes 1 and 3 in the example shown above); however, Hubbell does not disclose cycles of synthesis of staggered start (for synthesizing the quality control probes) that are initiated at ***every progressive synthesis cycle*** during synthesis of the array, as recited in instant claim 47. In fact, it is impossible to synthesize quality control probes in such fashion by the method described in Hubbell. The only way according to Hubbell's method to

synthesize quality control probes of staggered start is as depicted for synthesizing probes 1 and 3; i.e., where the synthesis cycles of those quality control probes differ by at least one repeating unit of synthesis cycle (e.g., ACGT) in the predetermined order of the monomer addition cycles; however this does not permit initiation of synthesis of the quality control probe at every progressive synthesis cycle. The method of Hubbell relies upon the predetermined order of the monomer addition cycles. Unlike the first nucleotide addition cycle of Hubbell where ***only*** an Adenosine (A) is added, the second nucleotide addition cycle allows only the addition of a Cytosine (C). According to Hubbell's method, only the same type of nucleotide can be added in each nucleotide addition cycle. Thus, it is impossible to synthesis a probe of ACGT which was initiated in the second nucleotide addition cycle. Therefore, there is no disclosure of synthesis of quality control probes whose synthesis is initiated by "different cycles of synthesis of staggered start, wherein said respective different cycles of synthesis of staggered start are initiated at ***every progressive synthesis cycle*** during synthesis of the array."

Moreover, the array produced by such a synthesis method as recited in claim 47 is not disclosed by Hubbell since the array of claim 47 will contain at least a plurality of quality control probes equal in number to the number of cycles of synthesis of the array; the numbers of cycles of synthesis of the array are clearly those number of cycles needed to generate the longest non-quality control probe on the array.[2] For example, Figure 3A of the specification depicts a quality control probe for ***each*** of the 36 consecutive progressive synthesis cycles of staggered start, covering cycle 0 to cycle 35. Hubbell does not disclose the use of an array containing such a number of quality control probes. Moreover, Hubbell teaches away from using at least a plurality of quality control probes equal to the number cycles of synthesis of the array. For example, Hubbell expressly states:

> but it is also preferable that the control probes do not occupy too much real estate on the chip. It is therefore desirable to utilize as few of probes a [sic] possible to evaluate the integrity of as many cycles as possible, preferably all cycles

(Hubbell, column 7, lines 32-36). Hubbell further teaches methods for optimizing quality probe design in order to achieve this goal. See, for example, Figures 6-8 of Hubbell. Indeed, in Hubbell's example at column 6, line 52 to column 7, line 29, quality control probes are ***not*** initiated at cycles 2-4 and 68, and 5 quality control probes are produced in 8 cycles. Thus,

[2] The total number of quality control probes on the array can be greater than the number of cycles of synthesis, but per the claim language of claim 47, the array must contain at least a plurality of quality control probes equal in number to the number of synthesis cycles, since the quality control probes in such plurality are initiated at every progressive synthesis cycle during synthesis of the array.

Hubbell does not disclose the method of claim 47. Therefore, claim 47 also is not anticipated by Hubbell.

Moreover, claim 48 depends on claim 47 and recites "before step (a) a step of synthesizing said array," which further distinguishes claim 48 from Hubbell, since, as discussed above, Hubbell does not disclose the method recited in claim 47 of synthesizing the plurality of quality control probes.

With regard to claim 54, the Examiner further contends that

> ... how the array is synthesized (i.e., by an inkjet) has no patentable weight as the method employs an array which is already synthesized. Since the array synthesized by Hubbell et al. anticipates the array of claim 54, the claim is anticipated.

(Office Action, page 5, fifth paragraph). Applicants respectfully disagree.

As discussed above and contrary to the Examiner's contention, the array synthesized by Hubbell is distinct from the array used in claim 54 for at least two reasons. Firstly, claim 54, like claim 47, specifies that the synthesis of the plurality of quality control probes is initiated with staggered start, at every progressive synthesis cycle during synthesis of the array. Thus, for all the reasons discussed above in connection with claim 47, the array used in claim 54 is not disclosed by Hubbell. Secondly, claim 54 specifies that at least a portion of the plurality of quality control probes is arranged in a periodicity of P, where P is the number of nozzles in an inkjet printhead. Hubbell does not disclose an array in which quality control probes are arranged in a periodicity, much less with a periodicity of P equal to the number of nozzles in an inkjet printhead. Therefore, Hubbell does not anticipate the method of claim 54.

New claim 56 also is not anticipated by Hubbell for at least the reason that claim 56 specifies that at least a portion of the quality control probes are arranged in a periodicity of P, which, as discussed above, is not disclosed by Hubbell. Thus, new claim 56 also is not anticipated by Hubbell.

As discussed above, Hubbell does not anticipate independent claims 6, 47, 54, and 56. Claim 9 depends from claim 6 and further comprises a step of synthesizing the array as recited in claim 6. New claim 55 depends from claim 54. New claim 57 depends from claim 56. Therefore, Hubbell does not anticipate claims 9, 55 and 57.

Accordingly, the Examiner's 35 U.S.C. § 102 rejection of claims 5, 6, 9, 42, 47, 48, and 54 should be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 103(a) of CLAIMS 7, 8, 10, 43, 49, AND 53 SHOULD BE WITHDRAWN

Claims 7, 8, 10, 43, 49, and 53 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hubbell in view of United States Patent Number 6,040,138, issued to Lockhart et al. on March 21, 2000 (hereinafter "Lockhart") (Office Action, page 6, second paragraph). Applicants respectfully disagree.

A finding of obviousness under 35 U.S.C. § 103 (a) requires a determination of the scope and the content of the prior art, the differences between the invention and the prior art, the level of the ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether one of ordinary skill in the art would have had a reasonable expectation that the claimed invention would be successful. *In re O'Farrell*, 853 F.2d 894, 902-4 (Fed. Cir. 1988); *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). An analysis under 35 U.S.C. § 103(a) "should be made explicit," and "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR International Co. v. Teleflex, Inc., et al*, 127 S.Ct. 1727, 1736 (2007).

Claim 7 has been canceled, obviating the rejection with respect to that claim. Claim 43 has been amended to depend on claim 40, also obviating the rejection. Claims 8 and 10 depend from claim 6, and claims 49 and 53 depend from claim 47; claims 6 and 47 were distinguished from the teachings of Hubbell as discussed above in response to the 35 U.S.C. § 102 rejection. In particular, regarding claim 6, Hubbell does not teach or suggest the use of an array containing quality control probes comprising spacer sequences that are contiguous with the predetermined binding sequence. Regarding claim 47, Hubbell does not teach or suggest use of an array containing quality control probes whose synthesis is initiated by different cycles of synthesis of staggered start, wherein said respective different cycles of synthesis of staggered start are initiated at ***every progressive synthesis cycle*** during synthesis of the array, since this results in an array containing at least a plurality of quality control probes equal to the number of cycles of synthesis needed to generate the longest non-quality

control probe on the array. Lockhart does not remedy these deficiencies of Hubbell, because Lockhart does not teach or suggest these missing elements.

Specifically, the Examiner contends that "Lockhart et al. disclose that microarrays are useful in detecting target nucleic acids, such as those derived from a sample comprising cellular RNA or mRNA (column 2, lines 56-58)" (Office Action, page 6, sixth paragraph) and that:

> [i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hubbell et al. with the teachings of Lockhart et al., thereby arriving at the invention as claimed for the following reasons.

(Office Action, page 7, first paragraph).

The Examiner further contends that:

> With regard to the detection of target nucleic acids such as mRNA or RNA or cDNA derived from mRNAs, such detection method involving microarrays have long been practiced and thus one of ordinary skill in the art would have been motivated to combine the teachings of Lockhart et al. with the teachings of Hubbell et al., thereby arriving at the invention as claimed.

(Office Action, page 8, second paragraph).

Lockhart generally "provides methods of monitoring the expression levels of a multiplicity of genes." However, Lockhart does not teach or suggest quality control probes with spacer sequences. Lockhart also does not teach or suggest arrays containing at least a plurality of quality control probes equal in number to the number of cycles of synthesis needed to generate the longest non-quality control probe on the array, which results from initiating synthesis of quality control probes by different cycles of synthesis *of staggered start, wherein said respective different cycles of synthesis of staggered start are initiated at every progressive synthesis cycle during synthesis of the array.* Thus, Lockhart does not remedy the deficiencies of Hubbell.

In a recent case, the Court of Appeals for the Federal Circuit stated that "a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis." *Ortho-Mcneil Pharm., Inc. v. Mylan Labs., Inc.*520 F.3d 1358, 1364 (2008). The court further stated:

> [t]he TSM test, flexibly applied, merely assures that the obviousness test proceeds on the basis of evidence--teachings, suggestions (a tellingly broad term), or motivations (an equally broad term)--that arise before the time of invention as the statute requires.

Id. at 1365.

As discussed above, Hubbell and Lockhart, alone or in combination, do not teach or suggest or provide any other reason to use arrays with quality control probes that have spacer sequences or quality control probes resulting from initiation of synthesis at different cycles of synthesis of staggered start at every progressive synthesis cycle. There is no such teaching or motivation before the making of the instant invention. Moreover, even assuming arguendo that one of ordinary skill in the art may be motivated to apply the methods of Lockhart to the analysis of Hubbell, combining the two references does not achieve the instant invention. As shown by the discussion above, the instantly claimed invention is not a combination of known elements. *C.f. KSR International Co. v. Teleflex, Inc., et al*, 127 S.Ct. 1727 (2007).

Referring to Hubbell and with regard to the determination of the binding ratio, the Examiner contends that Hubbell discloses "a clear awareness of one of ordinary skill in the art for various way [*sic*] of determining whether the synthesis defect occurred or not by comparing the intensities of the control probes." In particular, the Examiner contends that Hubbell teaches calculating "a mean intensities [*sic*] of all the control probes" and "cycle intensity differences ('CIDS')" (Office Action, page 7, second to fourth paragraphs). The Examiner further contends that:

> [c]omparing the intensities of two control probes by taking their ratio for determining differences is rudimentarily employed in statistical analysis and thus, it is respectfully submitted that one of ordinary skill in the art would have been clearly capable of arriving at the claimed method.

(Office Action, page 8, first paragraph). Applicants respectfully disagree.

These teachings of Lockhart do not remedy the deficiencies of Hubbell noted above. It is therefore irrelevant whether "comparing the intensities of two control probes by taking their ratio for determining differences is rudimentarily employed in statistical analysis."

Therefore, Hubbell and Lockhart, alone or in combination, do not render obvious the rejected claims.

Accordingly, Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 7, 8, 10, 43, 49, and 53 based on Hubbell and Lockhart be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 103(a) of CLAIMS 37-40, 44-46, AND 50-52 SHOULD BE WITHDRAWN

Claims 37-40, 44-46, and 50-52 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hubbell in view of United States Patent Number 6,232,072, issued to Fisher et al. on May 5, 2001 (hereinafter "Fisher"). Applicants respectfully disagree.

The Examiner concedes that Hubbell does not "explicitly disclose that the method be employed for inkjet fabrication of arrays." However, the Examiner proceeds to contend that: "Fisher et al. explicitly discloses that there are fabrication defects in microarrays produced by inkjet fabrication methods (column 2, lines 19-33)" and to conclude that:

> [i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hubbell et al. and the teachings of Fisher et al., thereby arriving at the invention as claimed for the following reasons.

(Office Action, page 8, seventh and eighth paragraphs).

As discussed above, Hubbell does not disclose or suggest the present invention as claimed in the independent claims 6 and 47. Regarding independent claim 40, Hubbell also does not teach or suggest using arrays containing quality control probes arranged in a periodicity as recited in claim 40, as discussed above in connection with claim 54. Claims 38, 39, 44, 45, 51 and 52 have been canceled, which renders moot any rejections of these claims. Claim 37 depends from claim 6. Claim 46 depends from claim 40. Claim 50 depends from claim 47. Thus, Hubbell does not disclose or suggest the invention of claims 37-40, 44-46, and 50-52, for reasons already discussed. The deficiencies of Hubbell are not remedied by Fisher.

Fisher discloses the method of inkjet printing and as the Examiner points out that:

> ... every component in an array deposition apparatus are [*sic*] subject to errors such as component failure or variances in its operating parameters within, or sometimes even outside of, normal tolerances for such component. For example, a dispensing head used to dispense fluid droplets to form the array, may have one or more jets which fail or which vary slightly in the size of the droplets dispensed..." (column 2, lines 19-25; Fisher et al.)

(Office Action, page 9, second paragraph). However, a disclosure that synthesis defect exists in microarrays produced by an inkjet printing process does not suggest the claimed methods of detecting such defects. Fisher does not teach use of arrays with quality control probes with spacer sequences. Fisher also does not teach use of arrays containing at least a plurality of quality control probes equal in number to the number of cycles of synthesis needed to generate the longest non-quality control probe on the array, resulting from quality control probes whose synthesis is initiated by different cycles of synthesis *of staggered start, wherein said respective different cycles of synthesis of staggered start are initiated at every progressive synthesis cycle during synthesis of the array.* Fisher does not teach use of arrays with quality control probes arranged in a periodicity. As such, Fisher does not remedy the

deficiencies of Hubbell. Since Fisher does not remedy the deficiencies of Hubbell, combining Hubbell and Fisher does not render obvious the instant invention.

To support that one of ordinary skill in the art would be motivated to apply the teaching of Hubbell to manufacturing processes other than the photolithographic patterning method of synthesizing microarrays (i.e., the VSLIP™ technology), the Examiner points out that:

> Hubbell et al. state that while their preferred embodiments are directed to methods that utilize VSLIP™ technology, ***explicitly state*** that their invention is **not limited to this technology and may be advantageously applied to other manufacturing processes.**" (column 3, lines 43- 46; Hubbell et al.)

(Office Action, page 8, last paragraph bridging over to page 9, first paragraph). Therefore, the Examiner concludes that:

> one of ordinary skill in the art would have been motivated to employ the teachings provided for by Hubbell et al. in the method of synthesizing arrays via inkjet technology for the purpose of making certain of quality of the arrays synthesized, arriving at the invention as claimed.

(Office Action, page 9, third paragraph). However, a mere disclosure of applicability to inkjet printing is no way hints or suggests at the particular methods claimed by Applicants in view of the deficiencies in teachings of the cited art elaborated above.

Accordingly, Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 37-40, 44-46, and 50-52 based on Hubbell and Fisher be withdrawn.

CONCLUSION

Applicant respectfully requests entry of the foregoing amendments and remarks into the file of the above-identified application. Applicant believes that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted, Reg. No. 42,873

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